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A SUMMARY OF SOME OF THE PATHOGENETIC MECHANISMS INVOLVED IN BOVINE ABORTION

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Introduction

The terminology used in this discussion coincides with that recommended by the committee on bovine reproductive nomenclature (36). Reproductive dysgenesis is an all-encompassing term used to describe all categories of reproductive failure regardless of cause and regardless of when these losses occur in the gestational period. Losses occurring from conception until embryonic differentiation is complete (approximately 45 days) are termed embryonic mortality. Those losses occurring during the fetal period, that is from differentiation until parturition, are divided into abortions and premature deliveries. An abortion is the expulsion before full term of a conceptus incapable of independent life, while a premature delivery is the expulsion before full term of a fetus capable of independent life.

In this presentation the magnitude and broad categories of reproductive dysgenesis will be discussed only briefly. More particularly, fetal losses associated with infections will be dealt with in more detail under the following headings:

a) Routes which infections may take from the environment to the fetus.
b) The principal sites of injury in the fetal-placental unit.
c) Some factors determining the principal sites of injury.
d) Some factors influencing the clinical consequences of infection.
e) Some clinical manifestations of *in utero* infections.

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Magnitude of Reproductive Dysgenesis

It has been reported by David *et al* (19) that, using healthy cows and fertile bulls, approximately 63 calves may be expected from 100 first inseminations. The losses which occur before 50 days are only occasionally noticed and may be easily missed by the manager. The incidence of fetal abortion and premature deliveries born dead, based on limited observations, is in the vicinity of seven to 12 per cent of those cows found to be pregnant between 30–50 days after breeding (35, 56, 86).

The Categories of Reproductive Dysgenesis

The losses occurring during the fetal period and during the period of differentiation may be placed into three broad categories based on their causes. These are genetic, environmental and infectious.

Genetic causes are considered here to include abnormalities of the chromosomes or genes which produce disease in the embryo or fetus. The portion of reproductive dysgenesis that is attributed to genetic factors varies with the investigation; however, there is some general agreement that it comprises from one third to two thirds of the losses occurring in the first four months of gestation (14, 27). Chromosomal abnormalities are the most readily detected genetic cause of losses. Equally lethal but less apparent limitations on life are present at the gene level (78). Including these would raise the numbers of genetically caused abortions to an even higher proportion of reproductive dysgenesis. Genetic factors are at this stage beyond our "routine diagnostic capability", except for some cases of known hereditary anomalies with characteristic gross abnormalities (Hereditary osteopetrosis in Aberdeen Angus (49)). The losses

in early gestation are least costly. Genetic losses are referred to by Bishop as the "elimination of faulty genetic experiments at low biologic cost" (9).

Environmental factors resulting in reproductive failure are numerous and include the effects of such things as faulty nutrition, age and condition of dam at service, exogenous hormones and miscellaneous toxic compounds. The proportion of losses in this category is not known.

The last category and the one to be discussed more fully consists of abortions and premature deliveries associated with infections in the dam or fetal-placental unit. In the years up to 1973, approximately 25% of the fetuses submitted at diagnostic laboratories were diagnosed as to the probable cause of death (39). Eighty to 90% of those diagnosed were attributed to infections. It should not be inferred from this that infection is the largest category, but rather that fetal death caused by infection is more frequently diagnosed.

Isolation of agents from a fetus does not necessarily mean that they have caused the death of the fetus, as many agents appear to pass through the fetal-placental unit and cause little damage (38, 69). Other agents, however, are capable of inflicting serious injury to the fetal-placental unit and thereby interrupting the normal course of the pregnancy. It is not the purpose of this presentation to go into the details of each of these. Specific examples will be used to illustrate various steps in the pathogenesis of fetal infections which lead to fetal illness followed by fetal death and expulsion, or to the birth of sick calves.

Routes which Infections may take from the Environment to the Fetus

Entry into the Dam

The agent must first enter the cow to get to the fetus. Suggested portals of entry for some of the more frequently encountered infections include the following:

a) dam's skin – *Brucella abortus* (12), *Corynebacterium pyogenes* (23).
b) conjunctiva – *Brucella abortus* (12), *Leptospira pomona* (13).
c) respiratory tract – infectious bovine rhinotracheitis (I.B.R.) (72), *Leptospira pomona* (13), bovine virus diarrhea virus (B.V.D.) (55).
d) oral cavity – *Brucella abortus* (12), listeriosis (22), *Leptospira pomona* (13).
e) vagina and cervix-*Campylobacter fetus* (75), *C. pyogenes* (46).

Once the infectious agent is in the dam, the disease process may or may not have clinical manifestations other than those affecting the reproductive tract. Some agents vary in this regard. *Listeria monocytogenes* may produce central nervous system disease and abortion concurrently, or, as is more common, the processes may occur separately (41). Certain organisms may directly invade the fetal-placental unit from the dam or may instead produce disturbances which indirectly affect the pregnancy. Examples include (a) fever (meningitis, mastitis, pneumonia), (b) toxemia (pyelonephritis), (c) circulatory failure (suppurative pericarditis), (d) hypoxia (pneumonia) and (e) endotoxemia (may occur in association with many of the above or alimentary tract infections).

Movement from the Dam to the Placenta

From the dam the infection may move to the placenta by at least three routes:

a) Hematogenous – this necessitates the organism surviving in the blood stream and can occur with listeriosis, brucellosis, aspergillosis, I.B.R. and B.V.D. infections.
b) From the uterus – it is speculated that *C. pyogenes*, *C. fetus* and possibly other agents may be present in the uterus before conception. Growth into the placenta occurs when conditions are appropriate, possibly in relation to the declining inflammatory cell population in the reproductive tract during pregnancy as opposed to during estrus (17, 34).
c) Ascending from the vagina, through the cervix – it is probable that the presence of many organisms isolated from fetuses is a result of an ascending infection to the placenta from the cervix and vagina (34, 75). This type of infection occurs commonly in man and probably in cows following disturbances of the cervical seal as in impending abortion and premature delivery due to other causes, or during parturition (7, 10). Certain agents grow preferentially in the placenta. *Brucella abortus* thrives in the presence of erythritol (66). This substance is found in high quantities in the placenta and fetal fluids. Certain fungi also grow more abundantly in the placenta. This is related to the presence of as yet unidentified placental extracts (18, 85).

Movement from the Placenta to the Fetus

Some infectious agents may travel directly to the fetus by the umbilical vein, while others

penetrate through the placenta, infecting the fetus by contamination of the amniotic fluid. *Aspergillus fumigatus* appears to infect the fetus incidentally as a result of natural expansion from placental colonization (53). In these cases, the surface of the fetus and umbilical cord are exposed to the organism, as are the pharynx and alimentary tract when the contaminated amniotic fluid is swallowed. Systemic infection of the fetus may therefore result. Swallowing of amniotic fluid first occurs around the second to third month of gestation (1). Abomasal contents are, therefore, usually a good source from which to isolate bacterial and mycotic agents in aborted fetuses.

Whether viruses pass directly to the fetus through the circulation or whether placental infection always occurs is not established and is probably variable, depending on viral virulence, number of viral particles, etc. (68). Viruses which are more readily isolated from the placenta than from the fetus and which can be fairly consistently isolated in the placenta before abortion occurs, suggest a period of residence in the placenta before travelling to the fetus. I.B.R. virus infections appear to fall into this category and may travel to the fetus by way of the fetal circulation or by the amniotic fluid (65).

Principal Sites of Lesions in the Fetal-Placental unit

In a survey of 50 aborted fetuses, the placenta, liver, eyelid, intestine, lung and spleen were the most frequent sites in which lesions were observed (53).

Placenta

Placental infections may occur with little observable gross injury and only subtle microscopic damage (I.B.R. infections) (21). Conversely, the placenta may be the most obvious site of injury, the presence of the organism being associated with marked necrosis and inflammation (*Aspergillus fumigatus*) (32). Bacterial infections invading the pregnant uterus from the cervix probably most often produce a placentitis (7).

Fetus

When infections enter the fetus by the umbilical vein, lesions may be first evident in the liver. This is frequently the case with I.B.R. and *L. monocytogenes* infections (22). Lesions may, however, develop simultaneously in many sites as the infection circulates (53).

When the organism travels to the fetus by traversing the amniotic fluid, gross and microscopic lesions are commonly seen in the skin. In mycotic abortions, gross lesions in the skin probably appear in about one third of the cases (33), while microscopic lesions in skin occur in a higher proportion (53). Marked meconium staining of skin is frequently observed in aborted fetuses, premature deliveries and dystocias.

Lesions and organisms present in the alimentary tract probably reflect an oral route of infection and are common with a wide variety of isolates, including I.B.R. virus, *Aspergillus fumigatus* and *E. coli* (54).

Lung lesions are very common and may be a manifestation of (a) systemic infection (parainfluenza-3 virus (PI-3)) (79), (b) organisms growing into the respiratory passages from amniotic fluid or (c) active inhalation of amniotic fluid containing microorganisms and meconium probably in association with fetal hypoxia (30, 53).

Impaired fetal oxygenation may reflect maternal hypoxia, maternal circulatory failure, interference in transplacental transfer of oxygen (as in placentitis or placental separation) or impairment in delivery of oxygen from the placenta to the fetal tissues. In babies this has been demonstrated in compression of the umbilical cord, cord abnormalities and in impaired fetal cardiovascular function (6). Similar events undoubtedly occur in bovine fetuses. When the fetus becomes hypoxic, several events may take place. It is hypothesized that redistribution of blood flow to vital organs occurs. Decreased oxygenation of non-vital organs brought about by vasoconstriction induces hyperperistalsis and sphincter relaxation in the fetal intestine. As a result, the fetus passes meconium, and the exposed portions of the fetus become stained. The fetus at this stage is in a state of "temporary compensated fetal distress" (well-oxygenated vital organs and peripheral hypoxia). If hypoxia continues, the fetus reaches the end of its compensatory equilibrium and enters a state of "decompensated fetal distress" (2). Weak ineffectual respiratory movements normally exhibited by the *in utero* fetus then become strong respiratory movements which are followed terminally by violent jerking movements (31). It is while the fetus is exerting strong respiratory movements that active inhalation of amniotic fluid and its contents takes place. Fetal bronchopneumonia may result. The above is well documented in man (4, 30, 51, 67). Mixed inflammatory cell exudates containing meconium and epithelial squames are commonly seen in airways in

aborted bovine fetuses (53). The prevalence of pneumonias in newborn calves resulting from infections acquired *in utero* is not established. Histological examination of the lungs from neonatal deaths associated with bronchopneumonia occasionally reveal meconium in airways suggesting *in utero* hypoxia. The direction of fluid flow in the fetal lung is somewhat controversial. The net flow is generally accepted to be out of the lung and towards the larynx (3, 8, 20, 47). The source of the infectious agent causing the pneumonia however is usually not established.

Meconium staining in a premature or term delivery may, therefore, indicate either a compensated or decompensated state. The phase in which the calf is when born will probably determine the outcome. In a study of infants conducted by Vidyasagar *et al* (82), three criteria were used to indicate meconium aspiration: 1) meconium in the oropharynx or tracheobronchial tree, 2) clinical evidence of respiratory distress and 3) radiographic evidence of aspiration. Of 32 infants which had at least two of the three criteria, 17 developed respiratory failure and nine of these died. All infants were given oxygen, antibiotics and other supportive therapy. Our observations in cattle would suggest that meconium staining of amniotic fluid during live delivery would be one indication for rapid removal of the fetus with minimal stress, perhaps by cesarean section.

Some Factors Determining the Principal Sites of Injury

The ability of the microorganism to cause injury is influenced in varying degrees by the dam, (species, state of health and previous antigenic experience), the stage of gestation and the infectious agent involved. The stage of gestation is important, as it determines the state of organogenesis, immune competence and the physical development of the fetus (size, thickness of skin, etc.). Examples of different effects resulting from infections at different stages of gestation have been observed in B.V.D. (15). Bovine viral diarrhea infections occurring when the gestation is less than 99 days usually result in abortion or absorption and may result in mummification or stillbirth (42). Infections from 90–200 days may prevent or alter hair growth. Budding of basal epidermal cells in the bovine fetus occurs as early as 90 days but is not complete until the third trimester. The location of hair loss may signify when infection by B.V.D. virus has occurred. The important factor is probably the availability of susceptible immature cell populations undergoing rapid growth (15). In cattle the period of maximum cerebellar growth is estimated to be between 133 and 162 days of gestation. Infections with B.V.D. virus during this stage may result in varying degrees of cerebellar degeneration and hypoplasia. This manifestation is probably the result of a combination of lesions involving viral affinity for mitotically active cell populations in the earlier stages of gestation and lesions in the developing vascular system in later stages (11). Similar observations have been made with other viruses (68).

The interaction of infectious agent and state of fetal immune competence is observed when B.V.D. infection occurs late in gestation. At this stage the only detectable reaction to the infection may be the development of antibody (15). These antibodies are thought to be fetal in origin, as antibodies do not normally cross the bovine placenta. The bovine fetus is immunologically competent to respond to many antigens by 150–175 days (74). Lennette (50), in his discussions on diagnostic virology, has illustrated the probability of reaching a diagnosis based on the isolation of the agent or the detection of antibody. Appropriate clinical material must be properly collected at the right stage of the illness or the abortion process. Viral isolation is more likely in early stages of infection, whereas antibody detection is more probable in the later stages.

Another factor to consider is that fetal infections occurring early in gestation may not manifest their effects until later. At this time fetal antibody may be the only specific evidence indicating which agent or agents have been present. Some immunoglobulin production occurs in most fetuses, but a marked rise in immunoglobulin levels occurs in fetuses experimentally infected (73). The presence of immunoglobulins, even though specific, is not sufficient alone to determine the cause of the observed disease process. Specific antibodies to more than one infectious agent have been found in several fetuses (24).

In contrast to B.V.D., I.B.R. virus causes extensive cell destruction in all stages of gestation but apparently abortion occurs most frequently in the last trimester (45, 64). Rapid killing of different cell populations precipitates fetal death rapidly and, in most cases, before an immune response is apparent (43). Bacterial infections may also result in widespread cell destruction (63). Other consequences of bacterial infections may include disseminated intravascular coagulation, fetal acidosis and hemolysis of red blood cells. Endotoxin pro-

duction by Gram-negative organisms, whether in the dam or the fetal-placental unit, may precipitate abortion or premature delivery. Endotoxin probably evokes a generalized synthesis of F prostaglandins (76). Prostaglandin F2α curtails the functional life of the corpus luteum over a broad time range in gestation and is also a factor in inducing parturition near term (84).

Factors Influencing the Clinical Consequences of Infection

The clinical manifestations of infections are also functions of several factors acting together simultaneously. Some of these have been discussed above. Injury caused by colonization of microorganisms in various tissues is reflected clinically not only by the characteristics of the particular organism and its ability to infect, but also by the necessity for the function of the affected organ *in utero*. Severe localized lesions such as interstitial pneumonias, extensive brain damage and intraventricular septal defects may be of little clinical consequence *in utero*, whereas after birth these conditions are frequently lethal (11, 79). Organisms causing placental, hepatic, endocrine and systemic circulatory lesions, however, interfere with vital functions *in utero* and may result in a clinical manifestation.

The clinical consequences of a placentitis, a sick fetus or any situation inflicting stress on the fetus are influenced by the stage of fetal development. In the cow the corpus luteum is necessary up until around 200 days of gestation and may be necessary for a complete birth process, including discharge of fetal membranes, until the normal gestation time is reached (26, 52). *In utero* infections may precipitate premature delivery in the last trimester of the gestation period. This is exemplified by the work of Osburn *et al* (62), where *Campylobacter (Vibrio) fetus* injected into the uterus of pregnant cows in the second trimester produced fetal death and autolysis followed by abortion. In the third trimester however, three out of four animals injected with the same levels of *Campylobacter fetus* were able to attain premature birth. Two of the three born alive were born sick and died within 30 minutes, the other was born alive at 256 days gestation and appeared healthy but was infected by *Campylobacter fetus*.

The endocrine changes associated with parturition or probably any prolonged fetal stress, such as a sick fetus, may be summarized as follows. Under the influence of substances from the fetal hypothalamus, the anterior pituitary releases ACTH. As the cortex of the adrenal responds, an increased level of cortisol results. The increased fetal cortisol is followed by rising maternal levels of prostaglandins F2α probably produced by the cow's uterus. At approximately the same time, rising levels of estrogen and declining levels of progesterone are found in the maternal circulation. Evidence indicates that in the cow the main source of progesterone is the ovary. Estrogen is formed by the placenta and by the maternal adrenal (83). It has been suggested that with increased estrogens and decreased progesterone levels in the maternal circulation, pressure on the cervix activates the release of oxytocin from the posterior pituitary. Increased prostaglandin F2α has a direct action on the myometrium. Prostaglandins activate the myometrium at the end of pregnancy and sensitize uterine muscle to oxytocin (16, 28). Plasma cortisol levels in the newborn calf are markedly elevated and may increase the susceptibility of the newborn calf to infection (25). This further emphasizes the need for colostrum in the newborn calf.

Some Clinical Manifestations of *in utero* Infection

Having considered some of the factors operating in a pregnancy, consideration will now be given to the clinical manifestations of infection. If the fetus dies *in utero*, it may be absorbed, macerated, autolysed, aborted, mummified or become emphysematous.

If the embryo dies in the first stages of pregnancy, the pregnancy may be maintained until the embryo is absorbed. At this stage of gestation the embryo or placenta are not producing hormones, and the presence of the embryo prevents the release of luteolytic factors from the uterus (29). The uterine contents in some way usually prevent this release until absorption is complete.

As gestation proceeds, death of the fetus before the fetal skin becomes thick and completely keratinized (around seven months in the cow) may result in mummification if persistent bacterial infection with putrefaction is absent (37, 71). If there is bacterial putrefaction at this stage, fetal maceration occurs.

Fetal autolysis may occur when a fetus dies too rapidly to secure premature delivery in the later stages of gestation or following death by various means in the second trimester. The factors determining whether a dead fetus will be autolysed or mummified in the late second and early third trimester are only poorly understood (70). After death it usually takes

from two to four days for a fetus to be expelled from the uterus, at which time autolysis is marked (43, 45, 62). A mummified fetus may remain *in utero* for several months. The mechanism precipitating expulsion in these cases obviously does not require an active role by the fetus and is not parturition.

If the fetus dies in the late stages of gestation or during parturition and is not expelled from the reproductive tract within 24–48 hours, an emphysematous fetus may result. Gas forming bacteria present in the vagina may quickly invade the fetal-placental unit as the cervix dilates.

The fetus approaching endocrine maturity responds to stress in a similar manner to animals after birth. In sheep, at 90–143 days gestation, maternal hemorrhage and maternal hypoxia provoked a rise in fetal ACTH (5). A rise in cortisol levels occurred in two fetuses, aged at 140 and 143 days gestation. Increased size of the fetal adrenal cortex, increased plasma corticoid levels and premature delivery have been observed in intrauterine infections in sheep (61). Prolonged fetal stress may, therefore, invoke preparations for parturition (44).

During the last stage of pregnancy, a sick or otherwise stressed fetus (hypoxia due to placentitis) may secure its own delivery but with three different results:

a) The fetus may be delivered alive and die. Death following delivery may be the consequence of a malformation compatible with intrauterine life but lethal after birth. The committee on bovine reproductive nomenclature has set the time at which a bovine fetus can survive at approximately 260 days (36). The exact stage at which a bovine fetus is physiologically capable of surviving probably varies with the circumstances surrounding the premature delivery. Parturitions induced prematurely with various compounds have calf survival rates varying from near normal survival after 268 days of gestation, all dead at day 215 and variable results in the 240–250 day range (40, 48). Lung development and the production of surfactant are considered to be limiting factors in premature delivery in babies. Lung maturity appears to be hastened after the administration of corticosteroid in both animals and man but is not without some hazards (80). The respiratory distress syndrome, a surfactant related condition, is considered less common in babies with *in utero* infections (60). This may also be related to cortisol levels. Many other factors including sex, maternal nutrition and method of delivery require consideration (59, 81).

b) The fetus may be delivered alive and fail to thrive. Failure to thrive after birth may be the consequence of a minor congenital malformation or of a persistent infection acquired *in utero*. Bronchopneumonias following aspiration of amniotic fluid containing meconium and microorganisms are of unknown prevalence in animals but are considered fairly common in human stillbirths and neonatal deaths (58). Histological examination of the lungs from neonatal deaths in calves with bronchopneumonia occasionally reveals meconium in airways. The birth of sick calves following intrauterine *C. pyogenes* infections has been observed (77). While evidence of intrauterine exposure resulting in enteric infections after birth is difficult to document, the prevalence of intestinal lesions and organisms in alimentary tracts of aborted fetuses is supportive (54).

c) A fetus may secure its own live delivery and thrive even when infected (62).

A fetus may fail to secure its own live delivery during the last stage of gestation if it is killed too rapidly for the necessary endocrine changes to take place (I.B.R. infection). Dystocia and death due to dystocia is also more prevalent when the fetus is sick (57).

Conclusions

The pathogenesis of some of the infectious causes of abortion and premature delivery have been traced through from entry of the organism into the dam to the consequences of its arrival in the fetus. The eventual purpose is to understand the processes involved in abortion and premature delivery in order to diagnose and decrease fetal losses using preventive methods.

A broad range of factors must be considered to determine the causes of fetal losses. A high diagnostic rate can only be achieved if procedures include a complete and accurate clinical history, attempts at agent isolation, and levels of specific antibodies coordinated with the gross and microscopic findings.

Summary

The pathogenesis of bovine abortion is discussed with emphasis of fetal losses occurring in association with infections. The routes which infections may take from the environment to the fetus, principal sites of injury in the fetal-placental unit, factors determining the principal sites of injury, factors influencing the clinical consequences of infection and

some of the usual clinical manifestations of *in utero* infections are discussed.

Résumé

L'auteur commente la pathogénèse des avortements bovins, en mettant l'accent sur la perte de fœtus attribuable à des infections. Il insiste, entre autres, sur les voies que les infections peuvent prendre pour atteindre le fœtus, les principaux sites d'atteinte de l'ensemble: fœtus-placenta, les facteurs qui déterminent les principaux sites où se développent les lésions, les facteurs qui influent sur les conséquences cliniques de l'infection et certaines des manifestations cliniques usuelles des infections *in utero*.

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References

1. Abramovich, D. R. Fetal factors influencing the volume and composition of liquor amnii. J. Obstet. Gynaec. Br. Commonw. 77: 865–877. 1970.
2. Abramovici, H., J. M. Brandes, K. Fuchs and I. Timor-Tritsch. Meconium during delivery: A sign of compensated fetal distress. Am. J. Obstet. Gynec. 118: 251–255. 1974.
3. Adams, F. H., D. T. Desilets and B. Towers. Control of flow of fetal lung fluid at the laryngeal outlet. Resp. Physiol. 2: 302–309. 1967.
4. Adamsons, K. and R. E. Myers. Perinatal asphyxia: Causes, detection and neurologic sequelae. Pediat. Clins N. Am. 20: 465–480. 1963.
5. Alexander, D. P., H. G. Britton, M. L. Forsling, D. A. Nixon and J. G. Ratcliffe. Pituitary and plasma concentrations of adrenocorticotrophin, growth hormone, vasopressin and oxytocin in fetal and maternal sheep during the latter half of gestation and the response to haemorrhage. Biol. Neonate 24: 206–219. 1974.
6. Assali, N. S., J. C. Dehaven and C. T. Barrett. Disorders of water, electrolyte, and acid-base balance. *In* Pathophysiology of Gestation, Vol. III. N. S. Assali, Editor. pp. 221–222. Ithaca, New York: Cornell University Press. 1972.
7. Benirschke, K. Routes and types of infection in the fetus and the newborn. Am. J. Dis. Child. 99: 714–721. 1960.
8. Biggs, J. S. G., T. J. Gaffney and H. M. McGeary. Evidence that fetal lung fluid and phospholipids pass into amniotic fluid in late human pregnancy. J. Obstet. Gynaec. Br. Commonw. 80: 125–129. 1973.
9. Bishop, M. W. H. Paternal contribution to embryonic death. J. Reprod. Fert. 7: 383–396. 1964.
10. Blanc, W. A. Pathways of fetal and early neonatal infection. J. Pediat. 59: 473–496. 1961.
11. Brown, T. T., A. De Lahunta, F. W. Scott, R. F. Kahrs, K. McEntee and J. H. Gillespie. Virus induced congenital anomalies of the bovine fetus. II. Histopathology of cerebellar degeneration (hypoplasia) induced by the virus of bovine viral diarrhea – mucosal disease. Cornell Vet. 63: 561–578. 1973.
12. Bruner, D. W. and J. H. Gillespie. Hagan's Infectious Diseases of Domestic Animals. 6th Edition. pp. 200–201. Ithaca, New York: Cornell University Press. 1973.
13. Bruner, D. W. and J. H. Gillespie. Hagan's Infectious Diseases of Domestic Animals. 6th Edition. p. 504. Ithaca, New York: Cornell University Press. 1973.
14. Carr, D. H. Chromosome anomalies as a cause of spontaneous abortion. Am. J. Obstet. Gynec. 97: 283–293. 1967.
15. Casaro, A. P. E., J. W. Kendrick and P. C. Kennedy. Response of the bovine fetus to bovine-viral diarrhea-mucosal disease virus. Am. J. vet. Res. 32: 1543–1562. 1971.
16. Comline, R. S., L. W. Hall, R. B. Lavelle, P. W. Nathanielsz and M. Silver. Parturition in the cow: Endocrine changes in animals with chronically implanted catheters in the foetal and maternal circulations. J. Endocr. 63: 451–472. 1974.
17. Corbeil, L. B., R. R. Corbeil and A. J. Winter. Bovine venereal vibriosis: Activity of inflammatory cells in protective immunity. Am. J. vet. Res. 36: 403–406. 1975.
18. Corbeil, M. J. and S. M. Eades. The effect of soluble extracts of bovine placenta on the growth of fungi implicated in bovine myotic abortion. Br. vet. J. 129: lxxv–lxxix. 1973.
19. David, J. S. E., M. W. H. Bishop and H. J. Cembrowicz. Reproductive expectancy and infertility in cattle. Vet. Rec. 89: 181–185. 1971.
20. Dawes, G. S., H. E. Fox, B. M. Leduc, G. C. Liggins and R. T. Richards. Respiratory movements and rapid eye movement sleep in the foetal lamb. J. Physiol., Lond. 220: 119–143. 1972.
21. Dellers, R. W. Infectious bovine rhinotracheitis virus induced abortion in cattle: Pathological and immunofluorescent investigations. 68th Annual Conference for Veterinarians. Cornell University. January 20–22, 1976.
22. Dennis, S. M. Comparative aspects of infectious abortion diseases common to animals and man. Int. J. Fert. 13: 191–197. 1968.
23. Dietz, V. O., K. Koch, H. Schwarz-Linek, F. Horsch and H. Nattermann. Die *Corynebacterium-pyogenes*-Infektion des Rin-

des. 2. Mitt: Zum vorkommen und zur klinik der pyogenes – wundinfektionen beim rind. Sonderdruck aus Monatshefte für Veterinärmedizin 21: 813–820. 1974.

24. DUNNE, H. W., S. M. AJINKYA, G. R. BUBASH and L. C. GRIEL, JR. Parainfluenza-3 and bovine enteroviruses as possible important causative factors in bovine abortion. Am. J. vet. Res. 34: 1121–1126. 1973.
25. EBERHART, R. J. and J. A. PATT, JR. Plasma cortisol concentrations in newborn calves. Am. J. vet. Res. 32: 1921–1927. 1971.
26. ESTERGREEN, V. L., O. L. FROST, W. R. GOMES, R. E. ERB and J. F. BULLARD. Effect of ovariectomy on pregnancy maintenance and parturition in dairy cows. J. Dairy Sci. 50: 1293–1295. 1967.
27. FECHHEIMER, N. S. Chromosome abnormalities and embryo death in farm animals. Vet. Rec. 90: 241–243. 1972.
28. FITZPATRICK, R. J. The endocrinology of parturition. *In* The Use of Prostaglandins in Veterinary Practice. pp. 21–29. Proceedings of a Symposium held at the National Agricultural Centre, Stoneleigh, February 1975. Upjohn Limited, Crawley, Sussex.
29. HEAP, R. B. Role of hormones in pregnancy. *In* Reproduction in Mammals, Book 3, Hormones in Reproduction. C. R. Austin and R. V. Short, Editors. pp. 73–105. Cambridge, England: University Press. 1972.
30. HELWIG, F. C. Congenital aspiration pneumonia in stillborn and newborn infants. Am. J. Obstet. Gynec. 26: 849–857. 1933.
31. HEMS, D. A. Palpable regular jerking movements of the human fetus: A possible respiratory sign of fetal distress. Biol. Neonate 23: 223–230. 1973.
32. HILL, M. W. M., C. E. WHITEMAN, M. M. BENJAMIN and L. BALL. Pathogenesis of experimental bovine mycotic placentitis produced by *Aspergillus fumigatus*. Vet. Path. 8: 175–192. 1971.
33. HILLMAN, R. B. Bovine mycotic placentitis in New York State. Cornell Vet. 59: 269–288. 1969.
34. HINTON, M. Bovine abortion associated with *Corynebacterium pyogenes*. Vet. Bull. 42: 753–756. 1972.
35. HOLT, A. F. Analysis of conception rates and other in artificial insemination. Vet. Rec. 64: 31–38. 1952.
36. HUBBERT, W. T., Chairman. Recommendations for standardizing bovine reproductive terms. Cornell Vet. 62: 216–237. 1971.
37. HUBBERT, W. T. Relationship of unkeratinized skin to bovine fetal mummification: An hypothesis. Can. J. comp. Med. 38: 203–206. 1974.
38. HUBBERT, W. T. Biology of bovine fetal infection. *In* Summaries, XX World Veterinary Congress. Vol. 2. p. 854. 1975.
39. HUBBERT, W. T., G. D. BOOTH, W. D. BOLTON, H. W. DUNNE, K. MCENTEE, R. E. SMITH and M. E. TOURTELLOTTE. Bovine abortions in five northeastern states, 1960–1970: Evaluation of diagnostic laboratory data. Cornell Vet. 63: 291–316. 1973.
40. JOCHLE, W. Corticosteroid-induced parturition in domestic animals. A. Rev. Pharmac. 13: 33–55. 1973.
41. JONES, S. M. and M. WOODBINE. Microbiological aspects of *Listeria monocytogenes* with special reference to Listeriosis in animals. Vet. Revs. Annot. 7: 39–68. 1961.
42. KENDRICK, J. W. Bovine viral diarrhea-mucosal disease virus infection in pregnant cows. Am. J. vet. Res. 32: 533–544. 1971.
43. KENDRICK, J. W. and O. C. STRAUB. Infectious bovine rhinotracheitis-infectious pustular vulvovaginitis virus infection in pregnant cows. Am. J. vet. Res. 28: 1269–1282. 1967.
44. KENNEDY, P. C. Interaction of fetal disease and the onset of labor in cattle and sheep. Fedn Proc. 30: 110–113. 1971.
45. KENNEDY, P. C. and W. P. C. RICHARDS. The pathology of abortion caused by the virus of infectious bovine rhinotracheitis. Pathologia vet. 1: 7–17. 1964.
46. KOLAR, J. *Corynebacterium pyogenes* as a cause of bovine abortion. Bull. Off. int. Epizoot. 60: 341–353. 1963.
47. LANMAN, J. T., A. SCHAFFER, L. HEROD, Y. OGAWA and R. CASTELLANOS. Distensibility of the fetal lung with fluid in sheep. Pediat. Res. 5: 586–590. 1971.
48. LAUDERDALE, J. W. Effect of corticoid administration on bovine pregnancy. J. Am. vet. med. Ass. 160: 867–871. 1972.
49. LEIPOLD, H. W., L. E. DOIGE, M. M. KAY and P. H. CRIBB. Hereditary osteopetrosis in Aberdeen Angus calves. I. Pathological changes. Annls Génét. Sél anim. 3: 245–253. 1971.
50. LENNETTE, E. H. Laboratory diagnosis of viral infections: General principles. Am. J. clin. Path. 57: 737–750. 1972.
51. MANDELBAUM, B. Gestational meconium in the high-risk pregnancy. Obstet. Gynec. 42: 87–92. 1973.
52. MCDONALD, L. E., S. H. MCNUTT and R. E. NICHOLS. On the essentiality of the bovine corpus luteum of pregnancy. Am. J. vet. Res. 14: 539–541. 1953.
53. MILLER, R. B. and P. J. QUINN. Observations on abortions in cattle: A comparison of pathological, microbiological and immunological findings in aborted foetuses and foetuses collected at abattoirs. Can. J. comp. Med. 39: 270–290. 1975.
54. MILLER, R. B. Intestinal lesions in aborted bovine foetuses. *In* Summaries, XX World Veterinary Congress. Vol. 2. pp. 851–852. 1975.
55. MILLS, J. H. L. and R. E. LUGINBUHL. Distribution and persistence of mucosal disease virus in experimentally exposed calves. Am. J. vet. Res. 29: 1367–1376. 1968.
56. MITCHELL, D. Bovine abortion – An analysis of 227 cases. Can. vet. J. 1: 337–343. 1960.
57. MORTEN, D. H. and J. E. COX. Bovine dystocia. A survey of 200 cases met with in

general practice. Vet. Rec. 82: 530–537. 1968.
58. NAEYE, R. L., W. S. DELLINGER and W. A. BLANC. Fetal and maternal features of antenatal bacterial infections. J. Pediat. 79: 733–739. 1971.
59. NAEYE, R. L., R. K. FREEMAN and W. A. BLANC. Nutrition, sex, and fetal lung maturation. Pediat. Res. 8: 200–204. 1974.
60. NAEYE, R. L., H. T. HARCKE, JR. and W. A. BLANC. Adrenal gland structure and the development of hyaline membrane disease. Pediatrics 47: 650–657. 1971.
61. OSBURN, B. I., M. DROST and G. H. STABENFELDT. Response of fetal adrenal cortex to congenital infections. Am. J. Obstet. Gynec. 114: 622–627. 1972.
62. OSBURN, B. I., G. H. STABENFELDT and L. L. EWING. Relation of plasma progesterone to mid and late term bovine abortion due to *Vibrio fetus* infection. J. Reprod. Fert. 20: 77–83. 1969.
63. OSEBOLD, J. W., J. W. KENDRICK and A. NJOKU-OBI. Abortion of cattle. Experimentally with *Listeria monocytogenes*. J. Am. vet. med. Ass. 227–234. 1960.
64. OWEN, N. V., T. L. CHOW and J. A. MOLELLO. Bovine fetal lesions experimentally produced by infectious bovine rhinotracheitis virus. Am. J. vet. Res. 25: 1617–1625. 1964.
65. OWEN, N. V., T. L. CHOW and J. A. MOLELLO. Infectious bovine rhinotracheitis: Correlation of fetal and placental lesions with viral isolations. Am. J. vet. Res. 29: 1959–1965. 1968.
66. PEARCE, J. H., A. E. WILLIAMS, P. W. HARRIS-SMITH, R. B. FITZGEORGE and H. SMITH. The chemical basis of the virulence of *Brucella abortus*. II. Erythritol, a constituent of bovine foetal fluids which stimulates the growth of *Br. abortus* in bovine phagocytes. Br. J. exp. Path. 43: 31–39. 1962.
67. PENNER, D. W. and A. C. MCINNIS. Intrauterine and neonatal pneumonia. Am. J. Obstet. Gynec. 69: 147–168. 1955.
68. PLOTKIN, S. A. Routes of fetal infection and mechanisms of fetal damage. Am. J. Dis. Child. 129: 444–449. 1975.
69. PREVEDCURAKIS, C. N., E. STRIGOU-CHARALABIS and D. B. KASKARELIS. Bacterial invasion of amniotic cavity during pregnancy and labour. Obstet. Gynec. 37: 459–461. 1971.
70. ROBERTS, S. J. The enigma of fetal mummification. J. Am. vet. med. Ass. 140: 691–698. 1962.
71. ROBERTS, S. J. Veterinary Obstetrics and Genital Diseases (Theriogenology). 2nd Edition. pp. 170–172. Ithaca, New York. 1971.
72. SATTAR, S. A., E. H. BOHL and A. L. TRAPP. Abortion in cattle caused by experimental infection with infectious bovine rhinotracheitis virus. Cornell Vet. 57: 438–454. 1967.
73. SAWYER, M., B. I. OSBURN, H. D. KNIGHT and J. W. KENDRICK. A quantitative serologic assay for diagnosing congenital infections of cattle. Am. J. vet. Res. 34: 1281–1284. 1973.
74. SCHULTZ, R. D. Developmental aspects of the fetal bovine immune response: A review. Cornell Vet. 63: 507–535. 1973.
75. SCHURIG, G. D., C. E. HALL, K. BURDA, L. B. CORBEIL, J. R. DUNCAN and A. J. WINTER. Infection patterns in heifers following cervicovaginal or intrauterine instillation of *Campylobacter (Vibrio) fetus venerealis*. Cornell Vet. 64: 533–548. 1974.
76. SKARNES, R. C. and M. J. K. HARPER. Relationship between endotoxin-induced abortion and the synthesis of prostaglandin F. Prostaglandins 1: 191–203. 1972.
77. SMITH, R. E. and I. M. REYNOLDS. *Corynebacterium pyogenes* keratitis in a newborn calf. Cornell Vet. 6: 591–595. 1971.
78. SPARKES, R. S. and B. F. CRANDELL. Inborn errors of metabolism. *In* Pathophysiology of Gestation. Vol. II. N. S. Assali, Editor. pp. 233–235. Ithaca, New York: Cornell University Press. 1972.
79. SWIFT, B. L. Bovine parainfluenza-3 virus. Experimental fetal disease. J. Am. vet. med. Ass. 163: 861–862. 1973.
80. TAEUSCH, JR., H. W. Glucocorticoid prophylaxis for respiratory distress syndrome: A review of potential toxicity. J. Pediat. 87: 617–623. 1975.
81. TALBERT, L. M., W. E. EASTERLING, JR. and H. D. POTTER. Maternal and fetal plasma levels of adrenal corticoids in spontaneous vaginal delivery and cesarean section. Am. J. Obstet. Gynec. 117: 554–559. 1973.
82. VIDYASAGAR, D., T. F. YEH, V. HARRIS and S. PILDES. Assisted ventilation in infants with meconium aspiration syndrome. Pediatrics 56: 208–213. 1975.
83. WAGNER, W. C., F. N. THOMPSON, L. E. EVANS and E. C. I. MOLOKWU. Hormonal mechanisms controlling parturition. J. Anim. Sci. 38: 39–57. 1974.
84. WENKOFF, M. S. Developments in veterinary science. The use of prostaglandins in reproduction. Can. vet. J. 16: 97–101. 1975.
85. WHITE, L. O. and H. SMITH. Placental localization of *Aspergillus fumigatus* in bovine mycotic abortion: Enhancement of spore germination *in vitro* by foetal tissue extracts. J. med. Microbiol. 7: 27–34. 1974.
86. WITHERS, F. W. Wastage and disease incidence in dairy herds. Vet. Rec. 69: 446–453. 1957.